

Description

The present invention relates to a process for preparing a rhodium-containing homogeneous hydrogenation catalytic system, to two compounds formed thereby, and to the use of the catalytic system for the stereoselective hydrogenation of the exocyclic methylene group of acid addition salts of 6-demethyl-6-deoxy-6-methylene-5-hydroxytetracycline (methacycline) to prepare α -6-deoxy-5-hydroxytetracycline (doxycycline).

Doxycycline is a wide-spectrum antibacterial agent, with widespread application in the treatment of numerous infections in humans and in animals. The hydrogenation of the exocyclic methylene group of methacycline can produce two epimers. The α -6-epimer is doxycycline, whilst the β -6-epimer, called 6-epi-doxycycline, is devoid of clinical utility. Thus, it is important that the hydrogenation does not co-produce this β -6-epimer. In fact, the British Pharmacopoeia 1980 established a limit for the content of 6-epi-doxycycline in doxycycline of 2%.

In the prior art, doxycycline was first described in 1960 in U.S. patent no. 3,200,149. Since that time many methods have been described for its preparation, in all of which modification of the catalytic system has been described as producing improved yields or a purer product. In the field of heterogeneous catalysis, U.S. patents nos. 3,444,198, 3,849,491, 3,954,862 and 4,597,904 and the report in Chemical Abstracts 86, 89476 f. (1977) of Hungarian Patent 12 042, have all taught improved methods for the preparation of doxycycline and its analogues.

The first use of homogeneous catalysis was described in U.S. patent no. 4,207,258 (Italian priority 1972), wherein the catalyst was a complex of rhodium with tertiary phosphine, arsine and stibine ligands. U.S. patent no. 3,962,331 extended the above process to the simultaneous reductive dehalogenation and hydrogenation of an 11a-halomethacycline. French patent no. 2,216,268 later disclosed the use of the same catalyst. Since that time, other patents have appeared such as U.S. patents nos. 3,907,890, 4,001,321 and 3,962,131, all describing variations in the catalytic system and claiming improved yields and stereospecificity.

The first homogeneous hydrogenation catalysts of the type of tertiary phosphine-hydrazino-rhodium complexes were described in U.S. patent no. 4,550,096. These were prepared either by reacting a rhodium salt, specifically rhodium trichloride, with a tertiary phosphine and a hydrazine, or by reacting a rhodium complex, such as tris(triphenylphosphine)chlororhodium, with a hydrazine. These complexes allowed the preparation of doxycycline containing less than 1% of the undesired 6-epi-doxycycline, in high yield using considerably less rhodium than had been taught in the prior art.

U.S. patent no. 3,463,830 describes the preparation of zero valent platinum and palladium catalysts, by the reduction of these metals from oxidation state II by the use of the reducing agent, hydrazine. The function of the hydrazine is merely as a reducing agent, and it is not incorporated into the catalyst so prepared. As will be described hereinbelow, the compounds of the present invention differ from those of U.S. patent no. 3,463,830 in that the hydrazine is incorporated into the rhodium complex as a ligand, and surprisingly the rhodium is not reduced to the zero oxidation state.

U.S. patent no. 3,956,177 describes compositions useful as hydroformylation catalysts, prepared by contacting an organorhodium halide with a hydrazine and a phosphorus-containing adjuvant, to form an intimate mixture thereof. It is stated in the specification that these catalysts are not compounds formed by the components of the mixture, and they are not described as useful for the hydrogenation of carbon/carbon double bonds, but as catalysts for hydroformylation reactions.

Our European patent application no. 283 615 describes the preparation of several members of the group of triphenylphosphine-hydrazino-chlororhodium complexes and their application in the preparation of doxycycline.

We have now found that when rhodium trinitrate is used instead of rhodium trichloride in the process described in U.S. patent no. 4,550,096, surprisingly the complexes formed are generally different from those obtained using rhodium trichloride. Thus, the catalytic system so formed comprises rhodium complexes having quite different formulae to those obtained when starting from rhodium trichloride, and is not analogous to the series containing chloride as the anionic ligand.

Furthermore, we have found that, especially on an industrial scale, the minimum effective quantity of catalyst needed to hydrogenate a methacycline acid addition salt to prepare doxycycline can be further reduced by about one half by using the new rhodium trinitrate catalytic system of the invention, in relation to the quantity necessary when rhodium trichloride is used to prepare the catalytic system described in U.S. patent no. 4,550,096. This is an extremely important advantage because of the very high cost of rhodium.

According to the present invention, therefore, there is provided a process for the preparation of a rhodium-containing homogeneous hydrogenation catalytic system, which comprises reacting a rhodium salt,

a hydrazine and a tertiary phosphine in a solvent under otherwise inert conditions, characterised in that the rhodium salt is rhodium trinitrate.

In the process of the invention, one mole of rhodium trinitrate, as the dihydrate, is reacted with one to two moles, or even with an excess, of a suitable tertiary phosphine, and from one to two moles, or an excess, of a suitable hydrazine, in a suitable solvent, at a temperature between room temperature and the reflux temperature of the medium, preferably under an inert atmosphere. The expression "suitable" denotes those compounds which do not interfere with the catalytic activity of the system.

Not all tertiary phosphines are suitable but simple experimentation will show which can be used satisfactorily. Triphenylphosphine and its para-chloro and para-fluoro derivatives, for example, yield efficient complexes, whilst other derivatives of triphenylphosphine, such as the ortho-methoxy or para-dimethylamino, give inefficient complexes.

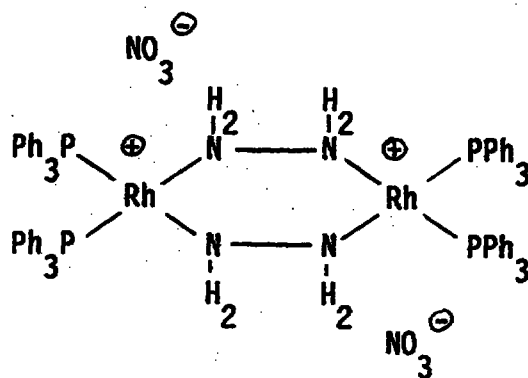
The suitable hydrazines are of the formula $R_1R_2N.NR_3R_4$, wherein R_1 is phenyl, benzenesulphonyl, lower alkyl or hydrogen and R_2 , R_3 and R_4 are lower alkyl or hydrogen, with the proviso that when R_1 is phenyl or benzenesulphonyl, R_2 , R_3 and R_4 are hydrogen. The preferred hydrazine is hydrazine itself and its hydrate.

The usual solvents are aliphatic alcohols containing one to four carbon atoms, the preferred solvent being methanol.

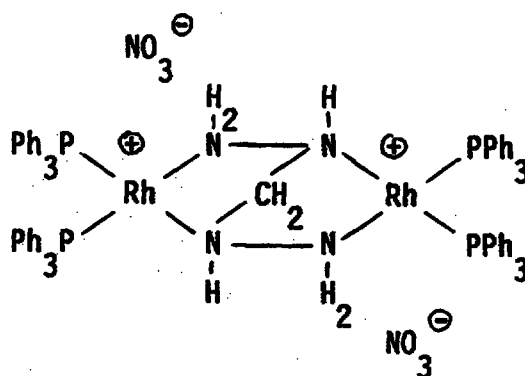
It has been found that the catalyst prepared "in situ" in the molar proportion of one mole of rhodium trinitrate dihydrate, one mole of triphenylphosphine and one mole of hydrazine does not have a satisfactory activity in the hydrogenation of methacycline p-toluenesulphonate to prepare doxycycline (α -epimer), in that the stereospecificity is reduced (7 α /1 β), whilst a molar proportion of 1:1:2 ensures a pronounced stereospecificity (24 α /1 β). A molar proportion of 1:1:3, results in an even higher stereo-specificity (45 α /1 β).

Generally, the preparation of the catalytic system of the present invention should be carried out using in total at least three moles of ligands, of which the tertiary phosphine must be present in one to two moles, for each mole of rhodium trinitrate.

By the process of the invention, certain new rhodium complexes can be formed. These new rhodium complexes, which are homogeneous hydrogenation catalysts, are formed when rhodium trinitrate dihydrate is reacted with triphenylphosphine and hydrazine, in degassed methanol under an inert atmosphere, one mole of rhodium trinitrate dihydrate being reacted with an excess of triphenylphosphine, preferably at least three and a half moles, and at least one mole of the hydrazine. The structures of the so-formed complexes of formulae I and II are:



(I)



(II)

wherein Ph is phenyl. The complex of formula I is predominant with short reaction times, and the complex of formula II is predominant with longer reaction times.

When the process of U.S. patent no. 4,550,096 is carried out in accordance with the present invention, that is using rhodium trinitrate, a mixture of products can be obtained. However, individual complexes can in general be obtained by carrying out the process under an inert atmosphere with complete exclusion of air and in degassed reaction media, followed by drying under an inert atmosphere or in vacuum. After eventual purification, the complexes can be obtained with uniform composition and well defined formulae.

Thus, the present invention includes within its scope the two complexes of formulae I and II, and their use in the hydrogenation of methacycline to furnish α -6-deoxy-5-hydroxytetracycline in high yield, near to stoichiometric.

When the process of the invention is carried out under an inert atmosphere, using for each mole of rhodium trinitrate dihydrate, an excess of triphenylphosphine, preferably at least three and a half moles, and at least one mole of hydrazine, in degassed methanol, a complex of formula I can be isolated after a short reaction time, typically of the order of one hour, and a complex of formula II can be isolated after longer reaction times, typically one to two days at room temperature. Alternatively, the reaction mixture can be refluxed overnight, followed by cooling and standing at room temperature.

The structures of the compounds of formulae I and II were established by X-ray crystallography.

The catalysts when prepared according to the conditions described above, are fully active in the hydrogenation of methacycline to doxycycline. Furthermore, it is not necessary to add excess triphenylphosphine to ensure a high yield of the required α -epimer.

The conditions of preparation of the catalysts of the present invention are illustrated in Examples 1 and 2. The rhodium trinitrate dihydrate and hydrazine can be reacted in the molecular proportion corresponding to their respective formulae, but it is advantageous to use hydrazine in excess so as to obtain the maximum yield in relation to the expensive rhodium salt.

The hydrazine can be used as either the anhydrous base or as the monohydrate. It has been verified that the anhydrous base allows shorter reaction times.

The triphenylphosphine is present in excess, preferably in a molar ratio of 3.5 in comparison with the rhodium present. This excess can be increased without any noticeable change in the products formed.

To achieve the best results in preparing the compounds of formulae I and II, rhodium trinitrate dihydrate

(1 mole), triphenylphosphine (3.5 moles) and hydrazine (3 moles) are mixed in degassed methanol under a nitrogen atmosphere. After stirring for 1 hour, a yellow crystalline solid of formula I is isolated by filtration and dried under vacuum. If the reaction mixture is stirred for a longer period, that is one to two days, an orange crystalline solid of formula II can be isolated by filtration and dried under vacuum. Alternatively, the reaction mixture can be refluxed over-night, followed by cooling and standing at room temperature.

The complexes of formulae I and II are stable for at least one month, providing they are stored under nitrogen at reduced temperatures. After this period, slightly diminished catalytic activity is sometimes observed. Therefore, these complexes should in preference be freshly prepared to obtain the best hydrogenation results. Alternatively, they can be prepared immediately prior to use and then employed without isolation, by addition to the hydrogenation reaction mixture, whereby equally good results can be achieved.

As already indicated, the hydrazino-rhodium complexes of the present invention are efficient homogeneous stereospecific hydrogenation catalysts, in general. The present invention however, has been specifically directed to their application in the hydrogenation of the exocyclic methylene group of 6-demethyl-6-deoxy-6-methylene-5-hydroxytetracycline present in the hydrogenation reaction mixture as an acid addition salt, so as to yield α -6-deoxy-5-hydroxytetracycline in a near stoichiometric yield.

The starting methacycline can be prepared by any of the known processes, such as that described in U.S. patent no. 3,849,491, but should not contain impurities which may act as a catalyst inhibitor.

Although the new complexes will catalyse the hydrogenation of methacycline base, the rate is so slow that the time of hydrogenation does not permit the yields obtained when using an acid addition salt.

The rate of hydrogenation increases with the temperature. Temperatures from ambient to 95°C can be used, but to achieve the best yields and stereospecificity, the optimum reaction temperature range is between 85°C and about 90°C. At 95°C the yields are slightly lower than for instance at 88°C. Below 85°C, the catalytic system starts to be sensitive to the eventual presence of certain trace impurities which may interfere with the rate of hydrogenation.

In the context of the hydrogenation of methacycline acid addition salts for the preparation of doxycycline, the present invention has several advantages when the temperature range during hydrogenation is 85°C to about 90°C. First, there is no necessity for extremely high hydrogen pressures. It has been found that from 1 kg/cm² to 10 kg/cm² will ensure complete conversion of the methacycline substrate in from 6 to about 10 hours. Typically, the hydrogenation is carried out at 88-89°C at a hydrogen pressure of 7 to 9 kg/cm² and is complete after 6 1/2 to 7 hours.

The painstaking preparation of the catalysts under strictly inert conditions can be alleviated by their preparation in degassed methanol under a nitrogen atmosphere immediately prior to use, followed by addition to the hydrogenation reaction mixture, after which the actual hydrogenation is carried out.

The transformation of the methacycline acid addition salt into doxycycline using the catalysts of the present invention, gives a purity above 95% in the reaction mixture, as analysed by high performance liquid chromatography (h.p.l.c.).

Additionally, the use of a rhodium to substrate ratio of 0.0002 by weight in laboratory scale experiments allows complete conversion within about 6 1/2 to 7 hours. On an industrial scale, a rhodium to substrate ratio of 0.00015 by weight is sufficient to permit complete conversion of the substrate within about 7 to 8 hours.

To ascertain the efficiency of the catalyst of formula II, large sized crystals were prepared, as described in Example 2. One of the crystals so obtained was used as catalyst in the hydrogenation of methacycline hydrochloride. The purity of the conversion of methacycline hydrochloride into doxycycline was 99.2%, with only 0.6% of the β -epimer being formed, as determined by high performance liquid chromatography.

In relation to U.S. patent no. 4,550,096, the most striking observation concerning the present invention lies in the fact that when the catalysts are prepared, dried, and stored under a strictly inert atmosphere, the catalysts exert full activity without the necessity of adding an excess of tertiary phosphine, more specifically triphenylphosphine, to the hydrogenation mixture so as to achieve the best yields.

An explanation for this is that the catalysts prepared according to the process of U.S. patent no. 4,550,096 were believed to be stable and, in fact, they exerted a very high catalytic activity, even when stored for long periods, because they were subsequently employed in the presence of a controlled excess of a tertiary phosphine. It is now believed that the catalysts prepared according to the process described in U.S. patent no. 4,550,096 oxidise slowly, but the presence of the excess tertiary phosphine in the hydrogenation reaction mixture, allowed substitution of the oxidised part of the tertiary phosphine, thereby regenerating the original catalytic system.

As has been previously mentioned, the catalyst is most conveniently prepared and used without isolation. Hydrazine (1 to 4 moles) is added with stirring to rhodium trinitrate dihydrate (1 mole) and

triphenylphosphine (3.5 moles) in degassed methanol in a glass vessel, under a nitrogen atmosphere. Upon addition of the hydrazine, the initial red colour turns to yellow. It is stirred for between a few minutes and two hours, and then transferred to the pressure reaction vessel containing the methacycline acid addition salt in methanol at 50 °C, under nitrogen.

Subsequently, the reaction vessel is purged again with nitrogen, then with hydrogen, finally being pressurised to 8 kg/cm² with hydrogen. The reaction mixture is heated to 88 °C under stirring, and the temperature maintained at 88 °C + 2 °C until the velocity of consumption of hydrogen slows down drastically, which occurs after about 6 to 7 hours. At this time, the reaction mixture contains nearly exclusively α -6-deoxy-5-hydroxytetracycline.

As is known in the art, the rate of the hydrogenation of methacycline is increased under acid conditions. Therefore, addition of an acid, preferably the same acid present in the acid addition salt of the substrate, will ensure high yields and purity. The amount of extraneous acid is not critical and it can be between one mole per mole of rhodium present up to about one mole per mole of the substrate to be hydrogenated. When the extraneous acid is not nitric acid, it is possible that the nitrate counter-ions of the compounds of formulae I and II, could be exchanged by the anion of the added acid.

The purity of the reaction mixture thus obtained is such that the doxycycline can be directly crystallised from the reaction mixture by adding excess p-toluenesulphonic acid, followed by cooling, yielding doxycycline p-toluenesulphonate with a purity superior to 99%.

The new catalytic system can also be employed in the simultaneous dehalogenation of the 11a-chloro-substituent and stereospecific hydrogenation of the 6-methylene group of 11a-chloromethacycline with good yields.

The following Examples serve to illustrate the present invention, without in any way limiting the scope thereof.

EXAMPLES

1. Preparation of di(μ -hydrazine-N¹:N²)-bis[bis(triphenylphosphine)-rhodium (I)] dinitrate

Rhodium trinitrate dihydrate (0.26 g; 0.85 mmoles) and triphenylphosphine (0.75 g; 2.86 mmoles) were placed in a two necked round bottom flask. They were stirred under vacuum for 30 minutes. Dry, degassed methanol (50 ml) was added, followed by 15 minutes stirring, to give an orange solution. The addition of hydrazine in methanol (7 ml of a 12.85 mg/ml solution; 2.81 mmoles) produced a bright yellow suspension which was stirred for a further 30 minutes. This yellow crystalline material was filtered off and dried under vacuum.

A number of attempts were made to select crystals for X-ray crystallographic analysis, but almost all samples selected were twinned. Eventually, a small fragment from a larger elongated parallelepiped was found which was single. This was used for collection of X-ray data on an Enraf-Nonius CAD4 diffractometer, following standard procedures. Details of the crystal data and structure determination are as follows:-

Crystal data: [C₇₂H₆₈N₄P₄Rh₂].[NO₃]₂.(CH₃OH)₂, Mw = 1507.19, monoclinic, space group C2/c with a = 24.431(3) Å, b = 13.480(2) Å, c = 22.102(3) Å, β = 94.27(2)°, V = 7258.8 Å³, Z = 4, D_c = 1.38 g.cm⁻³, μ -(Mo-K α) = 5.8 cm⁻¹

Data collection: Intensity data were collected in the range 1.5° ≤ θ ≤ 21.0° and a total of 4220 intensities were measured, of which 3883 were unique and 2336 were observed [$I > 3\sigma(I)$], and used in the analysis.

The structure was solved via the heavy-atom method, and refined by full matrix least squares. The phenyl groups in the phosphines were treated as rigid bodies. The current R value is 0.13, with all atoms refined in the isotropic approximation.

The structure contains a centrosymmetric dimeric cation in which two (PPh₃)₂Rh units are linked together by two bridging hydrazine molecules to produce a central Rh₂N₄ ring. By symmetry, this therefore has a chair conformation. The Rh-P and Rh-N distances are normal.

2. Preparation of μ -3-carbopentazane-N¹,N⁴:N²,N⁵-bis[bis(triphenylphosphine)rhodium (I)] dinitrate

Rhodium trinitrate dihydrate (0.36 g; 1.18 mmoles) and triphenylphosphine (1.12 g; 4.27 mmoles) were placed in a two necked round bottom flask. They were stirred under vacuum for 30 minutes and then under an atmosphere of nitrogen for 15 minutes. Dry, degassed methanol (100 ml) was added and the mixture stirred for 15 minutes. Hydrazine in methanol (10 ml of a 10.77 mg/ml solution; 3.36 mmoles) was added and the reaction mixture was refluxed overnight. The orange solution was filtered and stood at room temperature for 3 days, during which time large orange crystals were deposited. These were filtered off and

dried under vacuum.

When the reaction was repeated using rhodium trinitrate dihydrate (0.28 g; 0.91 mmoles), triphenylphosphine (0.80 g; 3.05 mmoles), hydrazine in methanol (8 ml of a 10.77 mg/ml solution; 2.69 mmoles) in methanol (60 ml) and stirring for two hours, clarification by filtration and standing for 5 days, similar orange crystals were obtained.

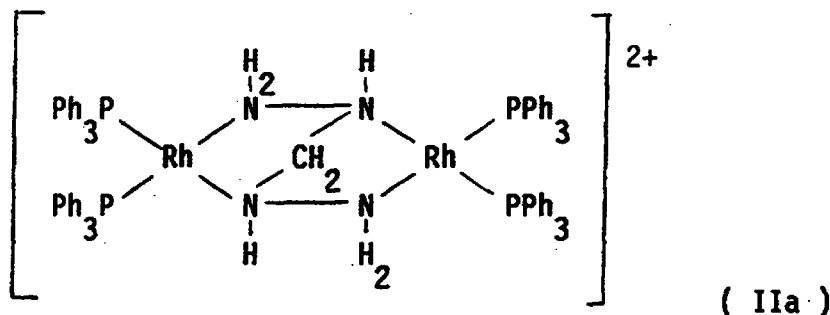
A single crystal of average diameter 0.4 mm was sealed under argon in a thin walled glass capillary. Unit cell and intensity data were obtained using an Enraf-Nonius CAD4 diffractometer, following standard procedures. Details of the experimental features are as follows:-

Crystal data: $[C_{73}H_{68}N_4P_4Rh_2].[NO_3]_2.(CH_3OH)_n$, $n \approx 0.5$, $M_w = 1455.10$ (excluding the methanol), monoclinic, space group $P2_1/n$, $a = 22.269(3)\text{\AA}$, $b = 23.311(3)\text{\AA}$, $c = 13.838(2)\text{\AA}$, $\beta = 100.51(2)^\circ$, $V = 7063.0\text{\AA}^3$, $Z = 2$, $D_c = 1.37\text{ g.cm}^{-3}$, $\mu(Mo - K\alpha) = 5.38\text{ cm}^{-1}$.

Data collection: Data were recovered for $1.5^\circ \leq \theta \leq 23^\circ$ at room temperature, 291°K and corrected for absorption empirically. 9820 intensities were measured, of which 7551 were observed [$I \geq 1.5\sigma(I)$], and used in the analysis.

The structure was solved via the heavy atom method and refined by full matrix least squares. All non-hydrogen atoms were refined with anisotropic thermal parameters, the phenyl groups being treated as rigid bodies. Hydrogen atoms on the phenyl groups were located experimentally, but for convenience were included and refined in idealised positions. Hydrogens on the bridging ligands were experimentally located and freely refined with isotropic thermal parameters. The final R value is 0.05 with 707 parameters.

The complex is shown to contain a dimeric cation in which two $(Ph_3P)_2Rh$ units were linked together by a 3-carbopentazane unit, as shown in IIa:-



The presence of the methylene bridge infers a boat conformation on the central Rh_2N_4 ring, with the bridge linking the "prow and stern" positions. The nitrate ions are well separated from the cation and do not appear to be forming any unusually close contacts. Indeed, one of them seems to occupy a cavity of such size that some positional disorder can occur, and it is also possible that a further cavity in the structure may be partially occupied by methanol of crystallisation.

In a repeat experiment, orange crystals of very similar morphology were obtained, but which appeared to suffer loss of crystallinity on removal from the methanol. On crystallographic examination, these were found to contain considerably more methanol of crystallisation, but the structure of the cation was found to be analogous to that in the first complex.

3. Hydrogenation of methacycline p-toluenesulphonate using a non-isolated catalyst

To a suspension of methacycline p-toluenesulphonate (9.50 g; 15.46 mmoles) in methanol (40 ml) was added a solution of rhodium trinitrate dihydrate (5.76 mg; 0.02 mmoles), triphenylphosphine (70.0 mg; 0.27 mmoles) and hydrazine hydrate (0.71 ml of a 0.0814M solution of hydrazine in methanol; 0.058 mmoles) in methanol (20 ml). This mixture was hydrogenated at a hydrogen pressure of 8 kg/cm^2 for 6 1/2 hours at 88°C . Thereafter, p-toluenesulphonic acid (3.3 g) was added to precipitate the doxycycline p-toluenesulphonate, which weighed 8.64 g, and had a purity of 98.72% by h.p.l.c.

4. Hydrogenation of methacycline hydrochloride using a non-isolated catalyst

To a suspension of methacycline hydrochloride (7.38 g; 15.41 mmoles) in methanol (40 ml) was added a solution of rhodium trinitrate dihydrate (5.90 mg; 0.02 mmoles), triphenylphosphine (19.1 mg; 0.07

mmoles) and hydrazine hydrate (0.47 ml of a 0.0814M solution of hydrazine in methanol; 0.038 mmoles) in methanol (20 ml). This mixture was hydrogenated at a hydrogen pressure of 8 kg/cm² for 6 1/2 hours at 89° C. Thereafter, p-toluenesulphonic acid (3.3 g) was added to precipitate the doxycycline p-toluenesulphonate, which weighed 9.08 g, and had a purity of 99.54% by h.p.l.c.

5. Hydrogenation of methacycline using μ -3-carbopentazane-N¹,N⁴:N²,N⁵-bis[bis(triphenylphosphine)-rhodium (I)] dinitrate

6-Demethyl-6-deoxy-6-methylene-5-hydroxytetracycline hydrochloride (10.38 g; 21.7 mmoles) was suspended in methanol (84.5 ml) in a stainless steel high pressure reaction vessel and μ -3-carbopentazane-N¹,N⁴:N²,N⁵-bis[bis(triphenylphosphine)rhodium (I)] dinitrate (25 mg; 0.017 mmoles; 0.034 mmoles of rhodium) was added under an atmosphere of nitrogen. The vessel was purged with nitrogen, then with hydrogen and pressurised to 8 kg/cm² with hydrogen. The reaction mixture was heated to 88° C for 6 1/2 hours with efficient stirring. The hydrogen was then discharged and p-toluenesulphonic acid (4.65 g; 24.2 mmoles) added under efficient stirring. The stirring was continued for 2 hours whereafter the resulting precipitate was filtered, washed with a small quantity of methanol and dried at 35° C.

The yield of α -6-deoxy-5-hydroxytetracycline p-toluenesulphonate was 12.0 g, or 89.8% of theoretical. By h.p.l.c., it was shown to be 99.2% pure.

20 Claims

Claims for the following Contracting States: AT, BE, CH, DE, FR, GB, GR, IT, LU, NL, SE

1. A process for the preparation of a rhodium-containing homogeneous hydrogenation catalytic system, which comprises reacting a rhodium salt, a hydrazine and a tertiary phosphine in a solvent under otherwise inert conditions, characterised in that the rhodium salt is rhodium trinitrate.
2. A process according to claim 1, wherein the tertiary phosphine is triphenylphosphine, the hydrazine is hydrazine itself or its hydrate, and the solvent is an aliphatic alcohol containing one to four carbon atoms.
3. A process according to claim 2, wherein the molar proportion of the reagents calculated for each mole of rhodium trinitrate dihydrate is from one to four moles of triphenylphosphine and from one to four moles of hydrazine hydrate, and wherein the solvent is degassed methanol.
4. A process according to claims 1, 2 or 3, wherein the catalytic system is prepared, under an inert atmosphere, by reacting the reagents at a temperature between room temperature and the reflux temperature of the medium.
5. A process according to claims 1, 2 or 3, wherein the catalytic system is prepared "in situ" in a hydrogenation reaction mixture.
6. A process according to claim 1, wherein rhodium trinitrate dihydrate, triphenylphosphine and hydrazine are reacted in the presence of degassed methanol under an inert atmosphere, to yield complexes of the formulae I and II:-



mmoles) and hydrazine hydrate (0.47 ml of a 0.0814M solution of hydrazine in methanol; 0.038 mmoles) in methanol (20 ml). This mixture was hydrogenated at a hydrogen pressure of 8 kg/cm² for 6 1/2 hours at 89° C. Thereafter, p-toluenesulphonic acid (3.3 g) was added to precipitate the doxycycline p-toluenesulphonate, which weighed 9.08 g, and had a purity of 99.54% by h.p.l.c.

5. Hydrogenation of methacycline using μ -3-carbopentazane-N¹,N⁴:N²,N⁵-bis[bis(triphenylphosphine)-rhodium (I)] dinitrate

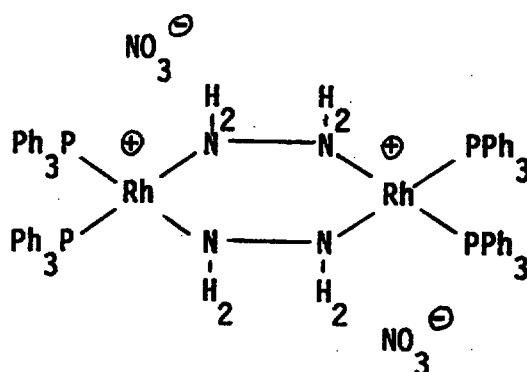
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The yield of α -6-deoxy-5-hydroxytetracycline p-toluenesulphonate was 12.0 g, or 89.8% of theoretical. By h.p.l.c., it was shown to be 99.2% pure.

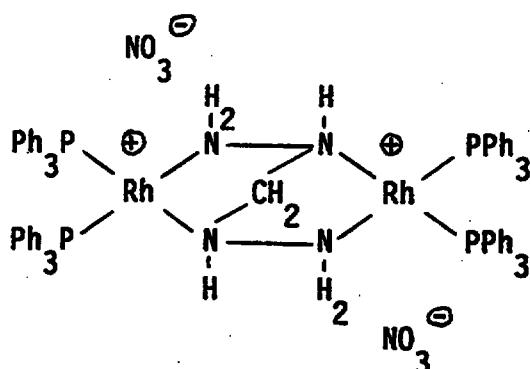
20 **Claims**

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1. A process for the preparation of a rhodium-containing homogeneous hydrogenation catalytic system, which comprises reacting a rhodium salt, a hydrazine and a tertiary phosphine in a solvent under otherwise inert conditions, characterised in that the rhodium salt is rhodium trinitrate.
2. A process according to claim 1, wherein the tertiary phosphine is triphenylphosphine, the hydrazine is hydrazine itself or its hydrate, and the solvent is an aliphatic alcohol containing one to four carbon atoms.
3. A process according to claim 2, wherein the molar proportion of the reagents calculated for each mole of rhodium trinitrate dihydrate is from one to four moles of triphenylphosphine and from one to four moles of hydrazine hydrate, and wherein the solvent is degassed methanol.
4. A process according to claims 1, 2 or 3, wherein the catalytic system is prepared, under an inert atmosphere, by reacting the reagents at a temperature between room temperature and the reflux temperature of the medium.
5. A process according to claims 1, 2 or 3, wherein the catalytic system is prepared "in situ" in a hydrogenation reaction mixture.
6. A process according to claim 1, wherein rhodium trinitrate dihydrate, triphenylphosphine and hydrazine are reacted in the presence of degassed methanol under an inert atmosphere, to yield complexes of the formulae I and II:-



(I)

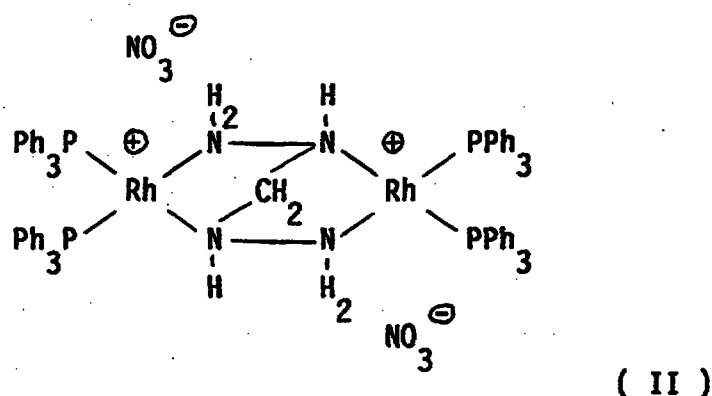
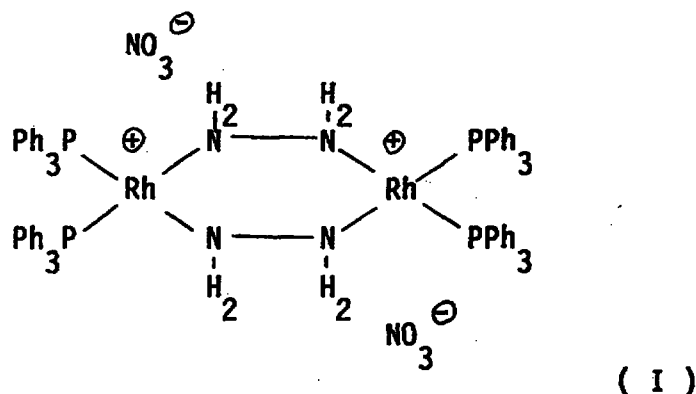


(II)

- wherein Ph is phenyl, using for each mole of rhodium trinitrate dihydrate, an excess of triphenylphosphine, preferably at least three and a half moles, and at least one mole of hydrazine.
7. A process according to claim 6, wherein the inert atmosphere is nitrogen.
 8. A process according to claims 6 and 7, wherein the hydrazine is the anhydrous base or the monohydrate.
 9. A process for the stereoselective hydrogenation of an acid addition salt of 6-demethyl-6-deoxy-6-methylene-5-hydroxytetracycline in the presence of a catalyst to prepare α -6-deoxy-5-hydroxytetracycline with a high yield and purity, characterised by the fact that the catalyst is a catalytic system prepared by the process of any of claims 1 to 8, and the hydrogenation is carried out at a temperature between 60°C and 100°C, at a pressure of 1 to 10 kg/cm² and under acid conditions, until the reaction is complete, followed by isolation of the thus formed compound by known processes.
 10. A process according to claim 9, wherein the hydrogenation is carried out at a temperature between 85°C and about 90°C.
 11. A process according to claim 9, wherein the catalyst has been prepared without isolation immediately prior to use, by reacting rhodium trinitrate dihydrate with three and a half moles of triphenylphosphine and with one to four moles of hydrazine, per mole of rhodium trinitrate dihydrate.
 12. A process according to claim 9, wherein three moles of hydrazine are used, per mole of rhodium trinitrate dihydrate.
 13. The compound di(μ -hydrazine-N¹:N²)-bis[bis(triphenylphosphine)-rhodium (I)] dinitrate.
 14. The compound μ -3-carbopentazane-N¹,N⁴:N²,N⁵-bis[bis(triphenylphosphine)rhodium (I)] dinitrate.


Claims for the following Contracting State : ES

1. A process for the preparation of a rhodium-containing homogeneous hydrogenation catalytic system, which comprises reacting a rhodium salt, a hydrazine and a tertiary phosphine in a solvent under otherwise inert conditions, characterised in that the rhodium salt is rhodium trinitrate.
2. A process according to claim 1, wherein the tertiary phosphine is triphenylphosphine, the hydrazine is hydrazine itself or its hydrate, and the solvent is an aliphatic alcohol containing one to four carbon atoms.
3. A process according to claim 2, wherein the molar proportion of the reagents calculated for each mole of rhodium trinitrate dihydrate is from one to four moles of triphenylphosphine and from one to four moles of hydrazine hydrate, and wherein the solvent is degassed methanol.
4. A process according to claims 1, 2 or 3, wherein the catalytic system is prepared, under an inert atmosphere, by reacting the reagents at a temperature between room temperature and the reflux temperature of the medium.
5. A process according to claims 1, 2 or 3, wherein the catalytic system is prepared "in situ" in a hydrogenation reaction mixture.
6. A process according to claim 1, wherein rhodium trinitrate dihydrate, triphenylphosphine and hydrazine are reacted in the presence of degassed methanol under an inert atmosphere, to yield complexes of the formulae I and II:-



wherein Ph is phenyl, using for each mole of rhodium trinitrate dihydrate, an excess of triphenylphosphine, preferably at least three and a half moles, and at least one mole of hydrazine.

7. A process according to claim 6, wherein the inert atmosphere is nitrogen.

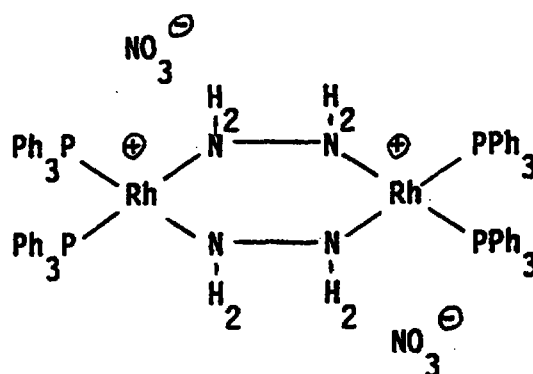


8. A process according to claims 6 and 7, wherein the hydrazine is the anhydrous base or the monohydrate.
9. A process for the stereoselective hydrogenation of an acid addition salt of 6-demethyl-6-deoxy-6-methylene-5-hydroxytetracycline in the presence of a catalyst to prepare α -6-deoxy-5-hydroxytetracycline with a high yield and purity, characterised by the fact that the catalyst is a catalytic system prepared by the process of any of claims 1 to 8, and the hydrogenation is carried out at a temperature between 60°C and 100°C, at a pressure of 1 to 10 kg/cm² and under acid conditions, until the reaction is complete, followed by isolation of the thus formed compound by known processes.
10. A process according to claim 9, wherein the hydrogenation is carried out at a temperature between 85°C and about 90°C.
11. A process according to claim 9, wherein the catalyst has been prepared without isolation immediately prior to use, by reacting rhodium trinitrate dihydrate with three and a half moles of triphenylphosphine and with one to four moles of hydrazine, per mole of rhodium trinitrate dihydrate.
12. A process according to claim 9, wherein three moles of hydrazine are used, per mole of rhodium trinitrate dihydrate.

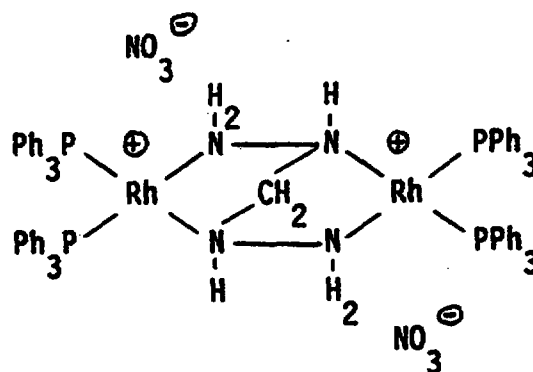
Revendications

Revendications pour les Etats contractants suivants: AT, BE, CH, DE, FR, GB, GR, IT, LU, NL, SE

1. Procédé de préparation d'un système catalytique d'hydrogénation homogène contenant du rhodium, qui comprend la réaction d'un sel de rhodium, d'une hydrazine et d'une phosphine tertiaire dans un solvant sous des conditions par ailleurs inertes, caractérisé en ce que le sel de rhodium est le trinitrate de rhodium.
2. Procédé suivant la revendication 1, caractérisé en ce que la phosphine tertiaire est la triphénylphosphine, l'hydrazine est l'hydrazine en tant que telle ou son hydrate et le solvant est un alcool aliphatique contenant 1 à 4 atomes de carbone.
3. Procédé suivant la revendication 2, caractérisé en ce que la proportion molaire des réactifs calculée pour chaque mole de dihydrate de trinitrate de rhodium est de 1 à 4 moles de triphénylphosphine et de 1 à 4 moles d'hydrate d'hydrazine et en ce que le solvant est du méthanol dégazé.
4. Procédé suivant l'une quelconque des revendications 1, 2 et 3, caractérisé en ce que le système catalytique est préparé, sous une atmosphère inerte, en faisant réagir les réactifs à une température entre la température ambiante et la température de reflux du milieu.
5. Procédé suivant l'une quelconque des revendications 1, 2 et 3, caractérisé en ce que le système catalytique est préparé "in situ" dans un mélange de réaction de l'hydrogénation.
6. Procédé suivant la revendication 1, caractérisé en ce qu'on fait réagir du dihydrate de trinitrate de rhodium, de la triphénylphosphine et de l'hydrazine en présence de méthanol dégazé sous une atmosphère inerte, de manière à obtenir des complexes des formules I et II :



(I)



(II)

formules dans lesquelles Ph représente un groupe phényle, en utilisant pour chaque mole de dihydrate de trinitrate de rhodium, un excès de triphénylphosphine, de préférence au moins trois moles et demie, et au moins une mole d'hydrazine.

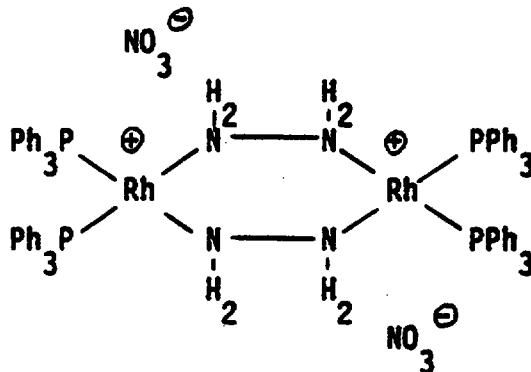
7. Procédé suivant la revendication 6, caractérisé en ce que l'atmosphère inerte est de l'azote.
8. Procédé suivant l'une ou l'autre des revendications 6 et 7, caractérisé en ce que l'hydrazine est la base anhydre ou le monohydrate.
9. Procédé d'hydrogénation stéréosélective d'un sel d'addition d'acide de la 6-déméthyl-6-désoxy-8-méthylène-5-hydroxytétracycline en présence d'un catalyseur pour préparer l' α -6-désoxy-5-hydroxytétracycline avec un rendement et une pureté élevés, caractérisé en ce que le catalyseur est un système catalytique préparé par le procédé suivant l'une quelconque des revendications 1 à 8 et en ce que l'hydrogénation est réalisée à une température comprise entre 60°C et 100°C, à une pression de 1 à 10 kg/cm² et sous des conditions acides, jusqu'à l'achèvement de la réaction, cette phase étant suivie par l'isolement du composé ainsi formé par des processus connus.
10. Procédé suivant la revendication 9, caractérisé en ce que l'hydrogénation est réalisée à une température comprise entre 85°C et environ 90°C.
11. Procédé suivant la revendication 9, caractérisé en ce que le catalyseur a été préparé sans isolement juste avant d'être utilisé, par la réaction de dihydrate de trinitrate de rhodium, de trois moles et demie de triphénylphosphine et d'une à quatre moles d'hydrazine par mole de dihydrate de trinitrate de rhodium.
12. Procédé suivant la revendication 11, caractérisé en ce que l'on utilise trois moles d'hydrazine par mole de dihydrate de trinitrate de rhodium.



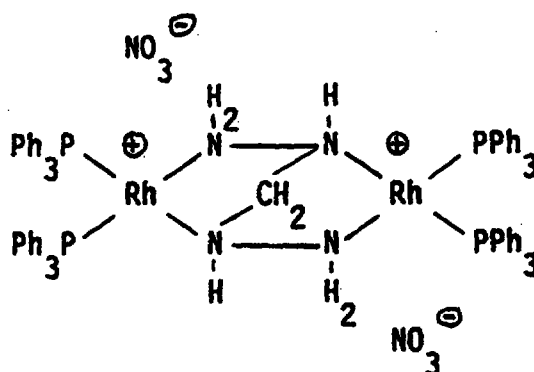
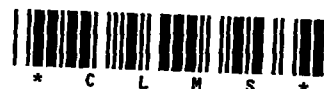
13. Le produit dinitrate de di(μ -hydrazine- $N^1:N^2$)-bis[bis(triphénylphosphine)rhodium (1)].
14. Le produit dinitrate de μ -3-carbopentazane- $N^1,N^4:N^2,N^5$ -bis[bis(triphénylphosphine)rhodium (1)].

5 Revendications pour l'Etat contractant suivant: ES

1. Procédé de préparation d'un système catalytique d'hydrogénation homogène contenant du rhodium, qui comprend la réaction d'un sel de rhodium, d'une hydrazine et d'une phosphine tertiaire dans un solvant sous des conditions par ailleurs inertes, caractérisé en ce que le sel de rhodium est le trinitrate de rhodium.
2. Procédé suivant la revendication 1, caractérisé en ce que la phosphine tertiaire est la triphénylphosphine, l'hydrazine est l'hydrazine en tant que telle ou son hydrate et le solvant est un alcool aliphatique contenant 1 à 4 atomes de carbone.
3. Procédé suivant la revendication 2, caractérisé en ce que la proportion molaire des réactifs calculée pour chaque mole de dihydrate de trinitrate de rhodium est de 1 à 4 moles de triphénylphosphine et de 1 à 4 moles d'hydrate d'hydrazine et en ce que le solvant est du méthanol dégazé.
4. Procédé suivant l'une quelconque des revendications 1, 2 et 3, caractérisé en ce que le système catalytique est préparé, sous une atmosphère inerte, en faisant réagir les réactifs à une température entre la température ambiante et la température de reflux du milieu.
5. Procédé suivant l'une quelconque des revendications 1, 2 et 3, caractérisé en ce que le système catalytique est préparé "in situ" dans un mélange de réaction de l'hydrogénation.
6. Procédé suivant la revendication 1, caractérisé en ce qu'on fait réagir du dihydrate de trinitrate de rhodium, de la triphénylphosphine et de l'hydrazine en présence de méthanol dégazé sous une atmosphère inerte, de manière à obtenir des complexes des formules I et II :



(I)



(II)

formules dans lesquelles Ph représente un groupe phényle, en utilisant pour chaque mole de dihydrate de trinitrate de rhodium, un excès de triphénylphosphine, de préférence au moins trois moles et demie, et au moins une mole d'hydrazine.

7. Procédé suivant la revendication 6, caractérisé en ce que l'atmosphère inerte est de l'azote.
8. Procédé suivant l'une ou l'autre des revendications 6 et 7, caractérisé en ce que l'hydrazine est la base anhydre ou le monohydrate.
9. Procédé d'hydrogénation stéréosélective d'un sel d'addition d'acide de la 6-déméthyl-6-désoxy-6-méthylène-5-hydroxytétracycline en présence d'un catalyseur pour préparer l' α -6-désoxy-5-hydroxytétracycline avec un rendement et une pureté élevés, caractérisé en ce que le catalyseur est un système catalytique préparé par le procédé suivant l'une quelconque des revendications 1 à 8 et en ce que l'hydrogénation est réalisée à une température comprise entre 60°C et 100°C, à une pression de 1 à 10 kg/cm² et sous des conditions acides, jusqu'à l'achèvement de la réaction, cette phase étant suivie par l'isolement du composé ainsi formé par des processus connus.
10. Procédé suivant la revendication 9, caractérisé en ce que l'hydrogénation est réalisée à une température comprise entre 85°C et environ 90°C.
11. Procédé suivant la revendication 9, caractérisé en ce que le catalyseur a été préparé sans isolement juste avant d'être utilisé, par la réaction de dihydrate de trinitrate de rhodium, de trois moles et demie de triphénylphosphine et d'une à quatre moles d'hydrazine par mole de dihydrate de trinitrate de rhodium.
12. Procédé suivant la revendication 11, caractérisé en ce que l'on utilise trois moles d'hydrazine par mole de dihydrate de trinitrate de rhodium.

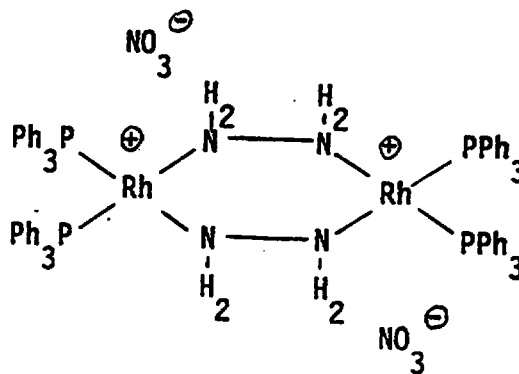
Patentansprüche

Patentansprüche für folgende Vertragsstaaten: AT, BE, CH, DE, FR, GB, GR, IT, LU, NL, SE

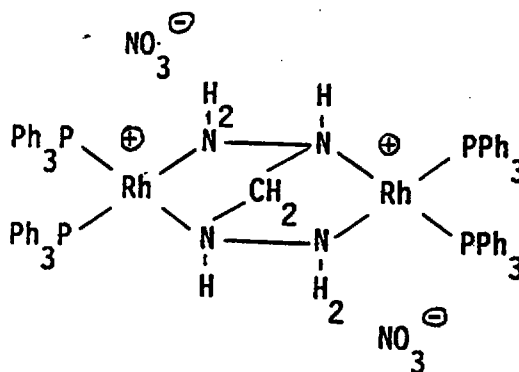
1. Verfahren zur Herstellung eines rhodium-haltigen, homogenen Katalysatorsystems zur Hydrierung, das die Umsetzung eines Rhodium-Salzes, eines Hydrazins und eines tertiären Phosphins in einem Lösungsmittel unter ansonsten inerten Bedingungen umfaßt, dadurch gekennzeichnet, daß das Rhodium-Salz Rhodiumtrinitrat ist.
2. Verfahren nach Anspruch 1, wobei das tertiäre Phosphin Triphenylphosphin ist, das Hydrazin Hydrazin selbst oder dessen Hydrat ist und das Lösungsmittel ein aliphatischer Alkohol mit ein bis vier Kohlenstoff-Atomen ist.
3. Verfahren nach Anspruch 2, wobei das Molverhältnis der Reagenzien bezogen auf ein Mol Rhodiumtrinitrat-dihydrat ein bis vier Mole Triphenylphosphin und ein bis vier Mole Hydrazinhydrat ist und wobei das Lösungsmittel entgastetes Methanol ist.



4. Verfahren nach Ansprüchen 1, 2 oder 3, wobei das Katalysatorsystem unter einer Inertatmosphäre durch Reaktion der Reagenzien bei einer Temperatur zwischen Raumtemperatur und der Rückflußtemperatur des Mediums hergestellt wird.
5. Verfahren nach Ansprüchen 1, 2 oder 3, wobei das Katalysatorsystem "in situ" in einer Hydrierungsreaktionsmischung hergestellt wird.
6. Verfahren nach Anspruch 1, wobei Rhodiumtrinitrat-dihydrat, Triphenylphosphin und Hydrazin in Gegenwart von entgasstem Methanol unter einer Inertatmosphäre zur Reaktion gebracht werden, unter Bildung von Komplexen mit den Formeln I und II:



(I)



(II)

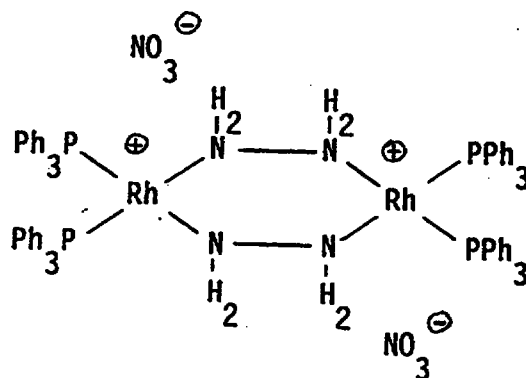
- 40 worin Ph Phenyl ist, wobei je Mol Rhodiumtrinitrat-dihydrat ein Überschuß an Triphenylphosphin, vorzugsweise wenigstens dreieinhalb Mole, und wenigstens ein Mol Hydrazin eingesetzt werden.
7. Verfahren nach Anspruch 6, wobei die Inertatmosphäre Stickstoff ist.
- 45 8. Verfahren nach Ansprüchen 6 und 7, wobei das Hydrazin die wasserfreie Base oder das Monohydrat ist.
9. Verfahren zur stereoselektiven Hydrierung eines Säureadditionssalzes von 6-Desmethyl-6-desoxy-6-methylen-5-hydroxytetracyclin in Gegenwart eines Katalysators zur Herstellung von α -6-Desoxy-5-hydroxytetracyclin in hoher Ausbeute und Reinheit, dadurch gekennzeichnet, daß der Katalysator ein Katalysatorsystem ist, hergestellt mit Hilfe des Verfahrens nach irgendeinem der Ansprüche 1 bis 8, und die Hydrierung durchgeführt wird bei einer Temperatur zwischen 60°C und 100°C, bei einem Druck von 1 bis 10 kg/cm² und unter sauren Bedingungen, bis zur Vollständigkeit der Reaktion, gefolgt von Isolierung der so gebildeten Verbindung mit Hilfe bekannter Verfahren.
- 55 10. Verfahren nach Anspruch 9, wobei die Hydrierung bei einer Temperatur zwischen 85°C und etwa 90°C durchgeführt wird.



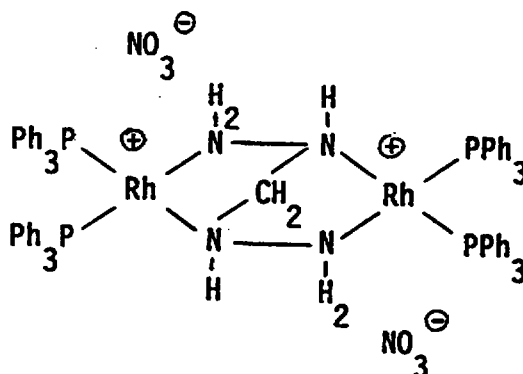
11. Verfahren nach Anspruch 9, wobei der Katalysator hergestellt wurde, ohne Isolierung unmittelbar vor Verwendung, durch Reaktion von Rhodiumtrinitrat-dihydrat mit dreieinhalb Molen Triphenylphosphin und mit einem bis vier Molen Hydrazin je Mol Rhodiumtrinitrat-dihydrat,
- 5 12. Verfahren nach Anspruch 9, wobei drei Mole Hydrazin je Mol Rhodiumtrinitrat-dihydrat verwendet werden.
13. Die Verbindung $\text{Di}(\mu\text{-hydrazin-}N^1:N^2)\text{-bis[bis(triphenylphosphin)rhodium(I)]-dinitrat}$.
- 10 14. Die Verbindung $\mu\text{-3-Carbopentazan-}N^1,N^4:N^2,N^5\text{-bis[bis(triphenylphosphin)rhodium(I)]-dinitrat}$.

Patentansprüche für folgenden Vertragsstaat: ES

- 15 1. Verfahren zur Herstellung eines rhodium-haltigen, homogenen Katalysatorsystems zur Hydrierung, das die Umsetzung eines Rhodium-Salzes, eines Hydrazins und eines tertiären Phosphins in einem Lösungsmittel unter ansonsten inerten Bedingungen umfaßt, dadurch gekennzeichnet, daß das Rhodium-Salz Rhodiumtrinitrat ist.
- 20 2. Verfahren nach Anspruch 1, wobei das tertiäre Phosphin Triphenylphosphin ist, das Hydrazin Hydrazin selbst oder dessen Hydrat ist und das Lösungsmittel ein aliphatischer Alkohol mit ein bis vier Kohlenstoff-Atomen ist.
- 25 3. Verfahren nach Anspruch 2, wobei das Molverhältnis der Reagenzien bezogen auf ein Mol Rhodiumtrinitrat-dihydrat ein bis vier Mole Triphenylphosphin und ein bis vier Mole Hydrazinhydrat ist und wobei das Lösungsmittel entgastes Methanol ist.
- 30 4. Verfahren nach Ansprüchen 1, 2 oder 3, wobei das Katalysatorsystem unter einer Inertatmosphäre durch Reaktion der Reagenzien bei einer Temperatur zwischen Raumtemperatur und der Rückflußtemperatur des Mediums hergestellt wird.
5. Verfahren nach Ansprüchen 1, 2 oder 3, wobei das Katalysatorsystem "in situ" in einer Hydrierungsreaktionsmischung hergestellt wird.
- 35 6. Verfahren nach Anspruch 1, wobei Rhodiumtrinitrat-dihydrat, Triphenylphosphin und Hydrazin in Gegenwart von entgastem Methanol unter einer Inertatmosphäre zur Reaktion gebracht werden, unter Bildung von Komplexen mit den Formeln I und 11:



(I)



(II)

- 30 worin Ph Phenyl ist, wobei je Mol Rhodiumtrinitrat-dihydrat ein Überschuß an Triphenylphosphin, vorzugsweise wenigstens dreieinhalb Mole, und wenigstens ein Mol Hydrazin eingesetzt werden.
7. Verfahren nach Anspruch 6, wobei die Inertatmosphäre Stickstoff ist.
- 35 8. Verfahren nach Ansprüchen 6 und 7, wobei das Hydrazin die wasserfreie Base oder das Monohydrat ist.
9. Verfahren zur stereoselektiven Hydrierung eines Säureadditionssalzes von 6-Desmethyl-6-desoxy-6-methylen-5-hydroxytetracyclin in Gegenwart eines Katalysators zur Herstellung von α -6-Desoxy-5-hydroxytetracyclin in hoher Ausbeute und Reinheit, dadurch gekennzeichnet, daß der Katalysator ein Katalysatorsystem ist, hergestellt mit Hilfe des Verfahrens nach irgendeinem der Ansprüche 1 bis 8, und die Hydrierung durchgeführt wird bei einer Temperatur zwischen 60°C und 100°C, bei einem Druck von 1 bis 10 kg/cm² und unter sauren Bedingungen, bis zur Vollständigkeit der Reaktion, gefolgt von Isolierung der so gebildeten Verbindung mit Hilfe bekannter Verfahren.
- 45 10. Verfahren nach Anspruch 9, wobei die Hydrierung bei einer Temperatur zwischen 85°C und etwa 90°C durchgeführt wird.
11. Verfahren nach Anspruch 9, wobei der Katalysator hergestellt wurde, ohne Isolierung unmittelbar vor Verwendung, durch Reaktion von Rhodiumtrinitrat-dihydrat mit dreieinhalb Molen Triphenylphosphin und mit einem bis vier Molen Hydrazin je Mol Rhodiumtrinitrat-dihydrat.
- 50 12. Verfahren nach Anspruch 9, wobei drei Mole Hydrazin je Mol Rhodiumtrinitrat-dihydrat verwendet werden.